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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/322,289	SCHENK, DALE B.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *6/27/06, 8/18/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-8,10-12,17,21-28,31-58,60-90 and 93-102* is/are pending in the application.

4a) Of the above claim(s) *25-28,33,34,38-58 and 60-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,4,6-8,10-12,17,21-24,31-32,35-37,82-90,93-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4,6-8,10-12,17-21-28,31-58,60-90,93-102* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

2. A complete listing of the claims which complies with 37 CFR 1.121 was filed 24 October 2005. No amendments were filed after the final rejection. The claims filed with the appeal brief on 27 June 2006 appear to be identical to those filed 24 October 2005. Prosecution is now reopened; the claims filed 24 October 2005 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

4. Claims 25 – 28, 33 – 34, 38 – 58, 60 – 81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 19 December 2000.

5. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are under examination.

Claim Objections

6. Claim 1 is objected to because of the following informalities: it appears to have a typographical error; line 3 of the claim includes the text "in a regime effective to or treat the disease" (emphasis added), which is confusing. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1 and 82 each recite "wherein the antibody is a chimeric or humanized antibody, or a human monoclonal antibody and the antibody is of isotype human

IgG1". It is unclear whether all antibodies encompassed by the claims are of isotype human IgG1, or whether this limitation only applies to "a human monoclonal antibody". It is unclear whether the scope of the claims includes chimeric or humanized antibodies of other isotypes or said antibodies generically. The remaining claims depend from rejected base claims and thus are rejected for being indefinitie as well.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering antibodies that specifically bind to Aβ peptide, does not reasonably provide enablement for treatment or prophylaxis of Alzheimer's disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case the nature of the invention, therapeutically or prophylactically treating Alzheimer's disease, is complex. The art recognizes that the disease has many features, including short-term memory loss, behavioral abnormalities, as well as a multitude of anatomical abnormalities such as the presence of both amyloid plaques and neurofibrillary tangles. Additionally, Alzheimer's disease is characterized by changes in permeability of the blood brain barrier; see Anderson (U.S. Patent 5,589,154), particularly column 6 lines 27 – 40, where the reference teaches that beta-amyloid protein, the causative agent in Alzheimer's diseases, also induces vascular damage. Treating any one of the symptoms of Alzheimer's disease, for

example the plaques, would not necessarily be expected to treat all of the symptoms. Disrupting the plaques, for example, may well lead to increased free beta-amyloid protein, which Anderson teaches will exacerbate the problems of vascular permeability. The art also recognizes that complete "treatment" of the disease is essentially impossible, although there are therapies which ameliorate certain symptoms of Alzheimer's. See Anderson, column 3, lines 56 – 60.

The specification, beginning on p. 70, discloses results of experiments in which antibodies raised against Aβ were administered to mice. Mice treated with PBS had significantly higher total Aβ in the cortex than mice treated with polyclonal antibodies (p. 73). PBS-treated mice had more Aβ 1-42 in the hippocampus than mice treated with antibody 10D5, which binds to residues 1-12. The differences approached, but did not reach statistical significance (p. 76). The totality of the evidence suggests that antibodies which bind to Aβ will decrease the amount of Aβ in the brain when administered peripherally. Thus the specification is enabling for decreasing the amount of Aβ in the brain.

However, the specification is not enabling for treatment, either therapeutic or prophylactic, as defined in the specification. The definition of the treatments appears at p. 27 of the specification and is reproduced below:

> IV. TREATMENT REGIMES
>
> In prophylactic applications, pharmaceutical compositions or medicants are administered to a patient susceptible to, or otherwise at risk of, a particular disease in an amount sufficient to eliminate or reduce the risk or delay the outset of the disease. In therapeutic applications, compositions or medicants are administered to a patient suspected of, or already suffering from such a disease in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a therapeutically- or pharmaceutically-effective dose. In both prophylactic and therapeutic regimes, agents are usually administered in several dosages until a sufficient immune response has been achieved. Typically, the immune response is monitored and repeated dosages are given if the immune response starts to fade.

Clearly, the definition of therapeutic treatment, which is on point to claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, includes curing of Alzheimer's disease. The definition of to cure includes the reversal of symptoms and restoration to health (see Merriam-Webster online

medical dictionary, entry for "cure", accessed 5 September 2006). Alzheimer's disease is characterized by death of cholinergic neurons. In order to cure the disease, which is included within applicant's definition of therapeutic treatment, the therapy would have to reanimate dead neurons. This is not shown in the specification, and the art recognized that it was impossible. Because the scope of claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37 includes curing the disease, the art recognized that this is impossible, and the specification provides no working examples of complete cures of the disease and does not provide sufficient guidance to the artisan as to how to perform such a cure, the artisan would have to undertake a very large degree of experimentation in order carry out the method over the full claimed scope. Given the lack of guidance in the specification and the complex nature of the invention, the degree of experimentation required would be undue.

Similarly, the specification (p. 27) defines a prophylactic treatment to include one that eliminates the risk of coming down with the disease. While the specification discloses that treatment with anti-Aβ antibodies decreases the number of plaques, it does not disclose prevention of all symptoms. The specification provides no working examples of complete prevention of the disease. The specification does not even provide guidance as to how prevention can be accomplished, or how the artisan could determine if the prophylactic methods of claims 82 – 90 and 93 – 102 had been accomplished. The specification does not disclose which patients are at risk of having the disease, nor does it disclose the amount of antibodies to be administered nor when the dosage should be administered to prevent the onset of symptoms. Since prophylaxis or prevention is to be performed on patients who do not yet have symptoms of the disease, it would be impossible to determine if patients who do not later come down with symptoms of the disease were successfully prevented from getting the disease, or whether they would not have gotten the disease even in the absence of prophylactic treatment. The specification does not disclose or provide guidance to the artisan how to determine if the method of prophylaxis is successful. Thus the artisan would have to determine how to devise such an assay of prophylaxis himself. Given the lack of guidance in the specification and the complex nature of the invention, the degree of experimentation required would be undue. Thus the specification is not enabling for prophylactic treatment as defined.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 – 2, 4, 11 – 12, 24, and 31 – 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001).

Becker teaches administration of antibodies which bind to A-beta for treatment of Alzheimer's disease (see column 7 lines 44 – 52). Becker's antibodies include chimeric and humanized antibodies (see column 5 lines 50 – 58). As set forth in the rejection under 35 USC 112, second paragraph above, the claim does not appear to require that the chimeric or humanized antibodies are of isotype IgG1. Note that the reference specifically teaches administration to humans for treatment of Alzheimer's (column 7). While claim 1 recites "a regime effective to ... treat the disease", no particular doses are recited within the claim and since the prior art reference teaches treatment, it is presumed to be "effective". Thus the reference anticipates claims 1 – 2, 4, 11, and 12. Claim 24 is rejected as Becker teaches administration in pharmaceutical compositions further comprising carriers (see column 8 lines 19 – 42). Claim 31 is rejected as the reference teaches that the antibodies are specific for Aβ protein in a β-sheet conformation (see column 5 lines 42 – 50) and further teaches that the protein only adopts this conformation after aging of the peptide in culture medium or water for at least 1 days (see paragraph spanning columns 2 – 3), therefore the antibodies which bind Aβ in β sheets would not be expected to bind full-length APP. Claim 32 is rejected as the reference teaches administration including intravenous (see column 8).

10. Claims 82 – 84, 87, 89 – 90, 97 – 99, and 102 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson (US 5,589,154, issued 31 December 1996), as evidenced by Cassel et al. (2001. Demography and Epidemiology of Age-Associated Neuronal Impairment. In: Functional Neurobiology of Aging, pp. 31 – 50).

Claim 82 and dependent claims encompass administration to patients displaying no symptoms of the disease, as they are drawn to prophylaxis and merely require administration to

"a patient", i.e. any patient and includes patients with no known risk factors for the disease (see for example dependent claim 87). Anderson teaches administration of antibodies which bind to Aβ; see column 16 lines 35 – 40 for example. Note that the antibodies of the invention can be humanized as recited in claim 82, and that Anderson specifically teaches the artisan how to make humanized antibodies (see column 12 lines 10 – 49). As set forth in the rejection under 35 USC 112, second paragraph above, the claim does not appear to require that the chimeric or humanized antibodies are of isotype IgG1. The definition of "prophylactic" treatment of disease provided at p. 27 of the specification appears to require that the patients be at risk of having the disease; the reference by Cassel provides evidence that this includes all people, as the risk of Alzheimer's disease increases with age (see particularly the end of p. 35 and Figure 4.3 on p. 36). Thus as all patients are at risk of having the disease, the reference by Anderson anticipates claim 82 as it teaches administration of the humanized antibody.

Claim 83 is rejected as the reference teaches administration to patients at risk of having Alzheimer's disease. Claim 84 is rejected as the reference encompasses administration to humans (see for example column 16 which discloses that human serum albumin is to be included, and also discloses treatment by paramedics and emergency room attendants, which is clearly directed to humans). Claim 87 is rejected as the reference teaches administration to patients with cerebral hemorrhage, but not to patients with known risk factors of Alzheimer's disease. Claims 89 – 90 are rejected as Anderson teaches administration of humanized antibodies, which are a form of chimeric antibodies. Claim 97 is rejected as Anderson teaches pharmaceutical compositions (see column 15 line 65 – column 16 line 34). Claim 98 is rejected as the antibodies are disclosed to be specific for Aβ and would not be expected to bind to full-length APP. Claim 99 is rejected as the references teaches administration via IV infusion (see column 16 lines 38 – 40). Claim 102 is rejected as Anderson teaches sustained release compositions comprising the antibody are also suitable for administration (see column 16 lines 12 – 34).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001).

The reasons why Becker anticipates claims 1 – 2, 4, 11 – 12, 24, and 31 – 32 are set forth in the rejection under 35 USC 102(b) above. However the reference does not teach human monoclonal antibodies as recited in claim 10, or the specific doses recited in claims 22 – 23 or the duration of administration as recited in claim 36.

It would have been obvious to one of ordinary skill in the art to use a human monoclonal antibody rather than a humanized monoclonal antibody, with a reasonable expectation of success. Becker teaches that methods of making antibodies in mammals generally are well-known (column 6 lines 10 – 21) and teaches that removing non-human sequences from the antibodies is advantageous because it leads to lower immunorejection (see column 6 lines 31 – 53). Becker teaches humanized antibodies are advantageous because they will elicit smaller adverse immune responses. While Becker does not explicitly teach administering human monoclonal antibodies, doing so would obviously result in even less of an adverse immune reaction such as immunorejection, as these antibodies would have no non-human sequence.

It would have been obvious to one of ordinary skill in the art to modify the method of Becker by adjusting the dose or duration of the administration protocol, with a reasonable expectation of success. The motivation to do so would be to more effectively treat Alzheimer's disease. See MPEP § 2144.05(II), which states that optimization of conditions through routine experimentation is not considered a contribution over the prior art and thus rejections under 35 USC § 103 are appropriate.

12. Claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 35 – 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001) in view of Miller (U.S. Patent 5,227,159 issued 13 July 1993).

The reasons why Becker anticipates or renders obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 are set forth in the rejections under 35 USC 102(b) and 103(a) above. However the reference does not teach monitoring the patient for antibody levels as recited in claim 35.

Miller teaches administration of anti-HIV antibodies for treatment of disease. Miller also

teaches measuring the levels of antibodies and repeating administration of the antibody as indicated by the circulating antibody levels (see column 15 lines 52 - 62), which is on point to claim 35. However Miller does not teach treatment of Alzheimer's disease by administration of antibodies which bind Aβ.

It would have been obvious to monitor antibody levels as taught by Miller, when treating Alzheimer's disease as taught by Becker. The motivation to do so would be to optimize the circulating level of antibody, thereby ensuring that a therapeutic dose was maintained.

13. Claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 35 – 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001) in view of Sabel (U.S. Patent 4,883,666, issued 28 November 1989).

The reasons why Becker anticipates or renders obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 are set forth in the rejections under 35 USC 102(b) and 103(a) above. However the reference does not teach sustained release compositions as recited in claim 37.

Sabel teaches implantation of controlled release systems for treatment of neurological diseases (see column 10 - column 12). Sabel teaches the implants are suitable for administration to patients with Alzheimer's disease (column 5 lines 5 - 26). However Sabel does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to implant a controlled release system to administer the antibodies, as taught by Sabel, with a reasonable expectation of success. Sabel teaches there are many advantages to implantation of controlled release systems, including constant predictable release and local administration, thereby obviating the need for high systemic doses (see column 2 lines 49 - 65).

14. Claims 1 – 2, 4, 6 – 8, 10 – 12, 22 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001) in view of Brookmeyer (1998. American Journal of Public Health 88:1337-1342).

The reasons why Becker anticipates or renders obvious claims 1 – 2, 4, 10 – 12, 22 - 24, 31 – 32, and 36 are set forth in the rejections under 35 USC 102(b) and 103(a) above. However the reference does not teach administering to patients under 50, as recited in claim 6, or patients with either inherited (claim 7) or no known (claim 8) risk factors.

Brookmeyer teaches that the incidence of Alzheimer's disease increases as people age, and further teaches that delaying onset or reducing severity even slightly would result in enormous savings, given the expected financial burden of the disease and the increasing percentage of the population that will live to old age. However Brookmeyer does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to use the method of Becker to treat patients under 50, or patients either with or without known risk factors, with a reasonable expectation of success. The motivation to do so would be to delay the onset of the disease, which would result in considerable savings.

15. Claims 1 – 2, 4, 10 – 12, 17, 22 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001) in view of Yachi (EP 0 285 159, published 10 May 1988).

The reasons why Becker anticipates or renders obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 are set forth in the rejections under 35 USC 102(b) and 103(a) above. However the reference does not teach administering a second antibody that binds to amyloid deposit as recited in claim 17.

Yachi teaches a second antibody that binds to Aβ protein. However Yachi does not teach administration for treatment of disease.

It would have been obvious to one of ordinary skill in the art to co-administer the antibodies from Becker and Yachi, with a reasonable expectation of success. It is *prima facie* obvious to co-administer two compounds known to be suitable for the same purpose (MPEP § 2144). Becker and Yachi teach antibodies that bind Aβ, and Becker teaches they are suitable for treatment of Alzheimer's.

16. Claims 1 – 2, 4, 10 – 12, 21 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001) in view of Zhang et al. (1998. Current Protocols in Molecular Biology 10.15.1 - 10.15.9).

The reasons why Becker anticipates or renders obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 are set forth in the rejections under 35 USC 102(b) and 103(a) above. The reference by Becker teaches labeled antibodies for detection, wherein the label is radioactive

(see column 8). However the reference does not teach heterologous peptides fused to the antibodies as recited in claim 21.

Zhang et al. teach labeling by epitope-tagging for detection of molecules. It would have been obvious to one of ordinary skill in the art to epitope tag the antibody of Becker, as taught by Zhang et al., with a reasonable expectation of success. A motivation to do so would be to detect the antibody in a heterogeneous sample. Becker teaches that their antibodies are useful for detection in diagnostic assays (see column 7). Because these are heterogenous samples using a labeled antibody as taught by Zhang is particularly useful, as the epitope allows for easy detection.

17. Claims 82 – 84, 87 – 90, 95 – 96, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US 5,589,154, issued 31 December 1996).

The reasons why claims 82 – 84, 87, 89 – 90, 97 – 99, and 102 are anticipated by Anderson are set forth in the rejection under 35 USC 102(b) above. However the reference does not teach administration of human monoclonal antibodies as recited in claim 88, or the specific doses recited in claims 95 – 96 or the duration of administration as recited in claim 101.

It would have been obvious to one of ordinary skill in the art to use a human monoclonal antibody rather than a humanized monoclonal antibody, with a reasonable expectation of success. Anderson teaches that methods of making antibodies in mammals generally are well-known (column 12) and teaches that removing non-human sequences from the antibodies is advantageous because it leads to a lower immune response. Anderson teaches humanized antibodies are advantageous because they will elicit smaller immune responses. While the reference does not explicitly teach administering human monoclonal antibodies, doing so would obviously result in even less of an immune reaction, as these antibodies would have no non-human sequence.

It would have been obvious to one of ordinary skill in the art to modify the method of Anderson by adjusting the dose or duration of the administration protocol, with a reasonable expectation of success. The motivation to do so would be to more effectively treat Alzheimer's disease. See MPEP § 2144.05(II), which states that optimization of conditions through routine experimentation is not considered a contribution over the prior art and thus rejections under 35 USC § 103 are appropriate.

18. Claims 82 – 84, 87 – 90, 95 – 96, and 100 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US 5,589,154, issued 31 December 1996) in view of Miller (U.S. Patent 5,227,159 issued 13 July 1993)

The reasons why Anderson anticipates or renders obvious the inventions of claims 82 – 84, 87 – 90, 95 – 96, and 101 – 102 are set forth in the rejections under 35 USC 102(b) and 103(a) above. However Anderson does not teach monitoring the patient for antibody levels as recited in claim 100.

Miller teaches administration of anti-HIV antibodies for treatment of disease. Miller also teaches measuring the levels of antibodies and repeating administration of the antibody as indicated by the circulating antibody levels (see column 15 lines 52 - 62), which is on point to claim 100. However Miller does not teach administration of antibodies which bind Aβ.

It would have been obvious to monitor antibody levels as taught by Miller, following administration as taught by Anderson. The motivation to do so would be to optimize the circulating level of antibody, thereby ensuring that the appropriate dose was maintained.

19. Claims 82 – 90, 95 – 96, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US 5,589,154, issued 31 December 1996) in view of Brookmeyer (1998. American Journal of Public Health 88:1337-1342).

The reasons why Anderson anticipates or renders obvious the inventions of claims 82 – 84, 87 – 90, 95 – 96, and 101 – 102 are set forth in the rejections under 35 USC 102(b) and 103(a) above. However Anderson does not teach administering to patients under 50, as recited in claim 85, or patients with inherited risk factors as recited in claim 86.

Brookmeyer teaches that the incidence of Alzheimer's disease increases as people age, and further teaches that delaying onset or reducing severity even slightly would result in enormous savings, given the expected financial burden of the disease and the increasing percentage of the population that will live to old age. However Brookmeyer does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to use the method of Becker to treat patients under 50, or patients either with or without known risk factors, with a reasonable expectation of success. The motivation to do so would be to delay the onset of the disease, which would result in considerable savings.

20. Claims 82 – 84, 87 – 90, 93, 95 – 96, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US 5,589,154, issued 31 December 1996) in view of Yachi (EP 0 285 159, published 10 May 1988).

The reasons why Anderson anticipates or renders obvious the inventions of claims 82 – 84, 87 – 90, 95 – 96, and 101 – 102 are set forth in the rejections under 35 USC 102(b) and 103(a) above. However Anderson does not teach administering a second antibody that binds to amyloid deposit as recited in claim 93.

Yachi teaches a second antibody that binds to Aβ protein. However Yachi does not teach administration for prophylaxis of disease.

It would have been obvious to one of ordinary skill in the art to co-administer the antibodies from Anderson and Yachi, with a reasonable expectation of success. It is *prima facie* obvious to co-administer two compounds known to be suitable for the same purpose (MPEP § 2144). Anderson and Yachi teach antibodies that bind Aβ, and Becker teaches they are suitable to be administered to patients for treatment of stroke.

21. Claims 82 – 84, 87 – 90, 94 – 96, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US 5,589,154, issued 31 December 1996) in view of Zhang et al. (1998. Current Protocols in Molecular Biology 10.15.1 - 10.15.9).

The reasons why Anderson anticipates or renders obvious the inventions of claims 82 – 84, 87 – 90, 95 – 96, and 101 – 102 are set forth in the rejections under 35 USC 102(b) and 103(a) above. Anderson teaches that when antibodies are administered to patients they can be labeled (column 13) and after such administration biological samples can be withdrawn and assayed for the presence of Aβ by detecting the antibodies. However Anderson does not teach heterologous peptides fused to the antibodies as recited in claim 94.

Zhang et al. teach labeling by epitope-tagging for detection of molecules. It would have been obvious to one of ordinary skill in the art to epitope tag the antibody of Anderson, as taught by Zhang et al., with a reasonable expectation of success. A motivation to do so would be to detect the antibody in a heterogeneous sample. Anderson teaches that their antibodies are useful for detection following administration to a patient. Because these are heterogenous samples using a labeled antibody as taught by Zhang is particularly useful, as the epitope allows for easy detection.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 19 of U.S. Patent No. 6,743,427. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the claims allow for administration of antibodies generically whereas in the issued claims the antibodies must bind a specific epitope of Aβ. Note that the issued claims encompass therapeutic and prophylactic treatment, administration of human IgG1 antibodies (see claim 1), as well as humanized (claim 7), chimeric (claim 15), and monoclonal antibodies (claim 8).

23. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected on the ground of nonstatutory obviousness-type double patenting as being

unpatentable over claims 1 – 36 of U.S. Patent No. 6,761,888. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the claims allow for administration of antibodies generically whereas in the issued claims the antibodies must bind a specific epitope of Aβ. Note that the issued claims encompass therapeutic and prophylactic treatment, (see claim 1), administration of human IgG1 antibodies (claim 19), as well as humanized (claim 14), chimeric (claim 15), and monoclonal antibodies (claim 17).

24. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 38 of U.S. Patent No. 6,913,745. Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in scope; the issued claims of the '745 patent are limited to administration of specific humanized antibodies whereas the instant claims are generic with respect to which antibodies are to be administered. Note that the issued claims encompass humanized (claims 12, 31), monoclonal (claims 16 and 35), and chimeric antibodies (claims 14 and 33).

25. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18 – 24 of copending Application No. 10/704,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in scope; claims 18 – 24 of the '070 application are limited to administration of specific humanized antibodies whereas the instant claims are generic with respect to which antibodies are to be administered.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 56 – 195 of copending Application No. 10/828548. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case they encompass administration of antibodies which bind to Aβ protein for treatment

or prevention of Alzheimer's disease. Note that in the '548 case claims 69, 83, 100, 108, and 112, amongst many others specifically encompasses monoclonal, humanized, and chimeric antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

27. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24 – 30 of copending Application No. 10/703,713. Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in scope; claims 24 – 30 of the '713 application are limited to administration of specific humanized antibodies whereas the instant claims are generic with respect to which antibodies are to be administered.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

28. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 46 of copending Application No. 10/890070. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the antibodies to be administered can bind to any epitope whereas in the '070 case they are limited to specific epitopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

29. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 133 – 136 of copending Application No. 10/232030. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the antibodies to be administered can bind to any epitope whereas in the '030 case they are limited to specific epitopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

30. Claims1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 52, 54 – 94, 138 – 163 of copending Application No. 10/923469. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the antibodies to be administered can bind to any epitope whereas in the '469 case some claims are limited to specific epitopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

31. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 46 of copending Application No. 10/890071. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the antibodies to be administered can bind to any epitope whereas in the '469 case the claims are limited to specific epitopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. Claims 1 – 2, 4, 6, - 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 164 – 204 of copending Application No. 10/923267. Although the conflicting claims are not identical, they are not patentably distinct from each other because in both cases the claims encompass treatment and prevention of disease by administering antibodies to Ab, including those that are chimeric (see for example claim 195 of '267 application).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

33. No claim is allowed.

34. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1) Adair et al. WO 91/16928. The reference teaches that the binding affinity of humanized antibodies which bind to ICAM-1 varies with isotype. IgG1 isotype binds more strongly than other isotypes, and this is due to the structure of the hinge and constant regions of IgG1. See especially pp. 22 – 23.

2) Kuby. 1997. Immunology, Third Edition, p. 123. The reference teaches the structure of human IgG isotypes and teaches that they vary in size and in the structure of the hinge region.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Daniel E. Kolker, Ph.D.
November 8, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER